Title

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Journal

Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research, 33(6)

ISSN

0884-0431

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Publication Date

2018-06-01

DOI

10.1002/jbmr.3391

ORIGINAL ARTICLE

JBMR

Association of Pre-ESRD Serum Calcium With Post-ESRD Mortality Among Incident ESRD Patients: A Cohort Study

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ABSTRACT

Albumin-corrected serum calcium (cSCa) decline at late stages of chronic kidney disease and rise after dialysis initiation. Although hypercalcemia is associated with higher mortality in end-stage renal disease (ESRD), there are scarce data on the impact of pre-ESRD cSCa on post-ESRD mortality. Therefore, we used a large national cohort of 21,826 US veterans who transitioned to dialysis in all US Department of Veterans Affairs health care facilities over 2009 to 2014 to examine the associations with all-cause and cause-specific post-ESRD mortality of (1) cSCa concentrations averaged over the last 6 months and (2) its rate of decline during the last 12 months before dialysis initiation. Mean concentrations and median rate of decline of cSCa were 9.3 ± 0.7 mg/dL and -0.15 (interquartile range -0.39 to 0.07) mg/dL/year, respectively. A total of 9596 patients died during the follow-up period (mean 1.9 years; total 41,541 patient-years) with an incidence rate of 23.1 per 100 patient-years. There was an independent linear association between higher cSCa with higher mortality ($p_{trend} < 0.001$). The mortality risk associated with cSCa $\geq$9.0 mg/dL was attenuated among active vitamin D users ($p_{interaction} < 0.001$). Patients with faster decline in cSCa showed lower mortality irrespective of baseline cSCa concentrations. These cSCa-mortality associations were stronger for noncardiovascular versus cardiovascular death. In conclusion, lower pre-ESRD cSCa and faster decline in cSCa were consistently and linearly associated with better post-ESRD survival among US veterans, especially for noncardiovascular death. Further studies are needed to determine if correcting hypocalcemia is beneficial or harmful and which intervention is preferred when indicated among patients transitioning to ESRD. © 2018 American Society for Bone and Mineral Research.

KEY WORDS: EPIDEMIOLOGY; DISORDERS OF CALCIUM/PHOSPHATE METABOLISM; STATISTICAL METHODS; DISEASES AND DISORDERS OF/RELATED TO BONE

Introduction

Calcium plays pivotal physiological and biochemical functions, including signal transduction, muscle contraction, neurotransmitter release, contribution to the coagulation cascade, and electrophysiologic stabilization of cell membranes, and therefore require tight regulation of levels in the body. In advanced chronic kidney disease (CKD), elevated fibroblast growth factor-23 and reduced functioning renal mass result in blunted activation of vitamin D in the kidney, leading to impaired intestinal calcium absorption and diminished renal tubular reabsorption.[1–4] Serum calcium concentrations are relatively maintained due to compensatory elevation of parathyroid hormone (PTH), which enhances bone resorption, but start declining at late stages of CKD.[3–5] Decreased serum calcium concentrations then rise after hemodialysis initiation,[6,7] likely because of positive calcium flux during dialysis, active vitamin D treatment, calcium-based phosphate binders, and/or secondary hyperparathyroidism.

In the dialysis population, serum calcium concentrations generally show a U- or J-shaped association with mortality.[8–10] Elevated extracellular calcium, along with hyperphosphatemia, are among established risk factors for vascular calcification and cardiovascular events,[11–13] the leading cause of death among

Received in original form July 11, 2017; revised form December 12, 2017; accepted January 5, 2018. Accepted manuscript online January 17, 2018.
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Additional Supporting Information may be found in the online version of this article.
Journal of Bone and Mineral Research, Vol. 33, No. 6, June 2018, pp 1027–1036
DOI: 10.1002/jbmr.3391

patients with CKD.[14] Meanwhile, a previous study of predialysis patients with stage 3–4 CKD showed a linear association between higher serum calcium concentrations and higher mortality risk.[15] Furthermore, there are no prior studies on the impact of pre-ESRD serum calcium concentrations in later stages of CKD, when hypocalcemia is most prevalent, upon post-ESRD mortality, largely because of the lack of large databases linking pre-ESRD transition data to post-ESRD registries.[16] The impact of therapeutic interventions that correct hypocalcemia upon post-ESRD outcomes also remains unclear. Therefore, we aimed to examine the interactions between pre-ESRD serum calcium concentrations, their rate of decline, related drugs (ie, calcium supplement and active vitamin D agents), and post-ESRD all-cause, cardiovascular, and noncardiovascular mortality in a large, nationally representative cohort of US veterans with incident ESRD.

Subjects and Methods

Study population and data source

The Transition of Care in CKD (TC-CKD) study is a historical cohort of US veterans with incident ESRD.[17–20] We included 64,930 veterans derived from the United States Renal Data System (USRDS) who transitioned to dialysis treatment from April 1, 2009, through March 30, 2014. In the current study, we included 24,227 patients with available data on serum calcium within 6 months before developing ESRD (Supplemental Fig. 1). We excluded 2434 patients who did not have serum calcium and albumin levels measured concomitantly and then 17 patients with errors in follow-up time. Our final analytical cohort consisted of 21,826 patients. This study was approved by the Institutional Review Boards of the Memphis and Long Beach Veterans Affairs Medical Centers. The requirement for written informed consent was waived because of the large sample size, patient anonymity, and nonintrusive nature of the study.

Demographic, clinical, and laboratory measurements

Baseline patient characteristics of the study cohort (including age, sex, race, and ethnicity) were drawn from a composite of USRDS Patient and Medical Evidence files, Veteran Affairs (VA) databases, and Centers for Medicare and Medicaid Services (CMS) databases, with the exception of marital status, which was collected from VA records. Preexisting comorbidity status was ascertained from VA and CMS data. For information on medication use, we collected data from CMS Medicare Part D files and VA pharmacy dispensation records. Individual medications were categorized into broad groups by clinician assessment. We defined 6-month medication ever-use as having a prescription filled within 6 months before dialysis initiation.

Data on the estimated glomerular filtration rate (GFR) at transition was primarily obtained from USRDS records and were supplemented with serum creatinine data obtained from the VA Corporate Data Warehouse (CDW) LabChem file and calculated with the CKD Epidemiology Collaboration formula.[21] Other laboratory data, including serum calcium and albumin measurements, were obtained from the Decision Support System National Data Extracts Laboratory Results file. Data on body mass index were obtained from the VA CDW Vital Signs file. In the present study, laboratory measurements were averaged over the 6-month period before ESRD transition and were considered to be baseline levels.

Exposure measurement

Our primary exposure was 6-month pre-ESRD (prelude) averaged cSCa. We computed cSCa with the following formula: corrected serum calcium = serum calcium + 0.8 × (4.0 − serum albumin) [if serum albumin <4.0 g/dL]. Concentrations of cSCa were then averaged over the 6-month prelude period and categorized into six groups: <8.0, 8.0 to <8.5, 8.5 to <9.0, 9.0 to <9.5, 9.5 to <10.0, and 10 or more mg/dL. In a sensitivity analysis, we examined uncorrected serum calcium as the exposure of interest including patients without data on simultaneously measured serum albumin.

The secondary exposure was the rate of change in cSCa over the period of 1 year before ESRD. The rate of change cSCa was calculated using mixed-effects models (ie, random intercept and random slope model) among 16,349 patients with ≥2 measurements during the 1-year pre-ESRD prelude period, in which the latest measurement had to be in the 6-month prelude period and at least 90 days after the first measurement. We divided cSCa slope into the following subgroups: <−0.4 mg/dL/year, −0.4 to <−0.2 mg/dL/year, −0.2 to <+0.2 mg/dL/year, and ≥0.2 mg/dL/year.

Outcome assessment

The main outcomes of interest for the retrospective cohort population were all-cause, cardiovascular, and noncardiovascular mortality after transition to dialysis. We extracted data for cause of death from USRDS records and categorized them into cardiovascular and noncardiovascular death. Information on censoring events, including death, were obtained from VA, CMS, and USRDS records. Follow-up started at the initiation of dialysis and continued until death, kidney transplantation, loss to follow-up, or the date of final follow-up assessment for all patients (September 2, 2014, for all-cause mortality [$n = 9596$] and June 30, 2014, for cardiovascular and noncardiovascular mortality [$n = 2913$ and 6284, respectively]).

Statistical analysis

Baseline characteristics of the study population were presented according to cSCa groups. We reported means ± standard deviation (SD) or median [interquartile range] for continuous variables, where appropriate, and percentages for categorical variables. Linear trends for baseline patient characteristics were tested across cSCa groups. Comparisons of baseline demographic, clinical, laboratory, and medication characteristics between patients with and without cSCa were done using standardized differences and are presented in Supplemental Table S1.

Potential confounders were included in four hierarchal models of adjustment: (1) model 1, unadjusted; (2) model 2 included age, sex, race, ethnicity, and marital status; (3) model 3 included all covariates in model 2 plus Charlson comorbidity index, diabetes, prior history of ischemic heart disease, congestive heart failure, atrial fibrillation, cerebrovascular disease, chronic pulmonary disease, depression, and cancer, serum albumin, body mass index, and estimated GFR; and (4) model 4 included all covariates in model 3 plus baseline medications, which were composed of calcium supplements, active vitamin D, nutritional vitamin D (either ergocalciferol or cholecalciferol), calcium-containing phosphate binders, erythropoiesis-stimulating agents, RAAS inhibitors, sodium bicarbonate, and loop and/or thiazide

diuretics. In analyses including slope as the predictor variable, the first available cSCa measurement in the 1-year period before ESRD transition was added as a covariate across all adjustment models. We defined model 3 as the primary model of interest.

Multinomial logistic regression models were used to assess the associations of demographic, clinical, and laboratory variables and medication use with the outcomes hypocalcemia defined as <8.5 mg/dL in relation to hypercalcemia defined as >10.0 mg/dL, and vice versa, 8.5 to 10.0 mg/dL (reference group), with adjustment for covariates in model 3. We examined mortality using Cox proportional hazards models. We also assessed whether the association between 6-month prelude cSCa concentrations and post-ESRD mortality varied by medication use (calcium supplement and active vitamin D agents) in adjustment model 3, using 12 combination groups of 6-month prelude medication ever- and never-use with six cSCa groups compared with the reference group (medication never-use and cSCa levels of 8.5 to <9.0 mg/dL). Restricted cubic spline functions were used to assess the associations between cSCa and slope modeled as continuous variables and post-ESRD all-cause, cardiovascular and noncardiovascular mortality, and across strata of race, medication use, and first available cSCa in adjustment model 3. Knots were placed at the 5th, 35th, 65th, and 95th percentiles. Formal tests for interaction were done using the Wald test.

We applied a mixed-effects regression model to evaluate the trajectory of monthly population mean cSCa concentrations over the period of 1-year pre- and post-dialysis initiation.

Missing data on demographics, including marital status, were less than 0.2% and were handled using a dummy category. For missing data (4.0% and 2.0% for body mass index [BMI] and estimated GFR, respectively), we employed the multiple imputation method where five data sets were created by using multivariate normal regression with all available data. In a sensitivity analysis, we examined uncorrected serum calcium as the exposure of interest including patients with data on cSCa but not on serum albumin ($n = 24{,}256$ versus 21,826 in the main cohort). For all analyses in this study, a two-tailed p value of less than 0.05 was considered statistically significant. Survival and logistic regression analyses were conducted with the use of SAS Enterprise Guide, version 7.1 (Cary, NC, USA). Restricted cubic spline functions and mixed-effects regression were conducted with STATA version 14.2 (StataCorp, College Station, TX, USA).

Results

Baseline demographic, clinical, and laboratory characteristics

A total of 21,826 US veterans with ESRD transitioning to dialysis were included in this study. The median time interval between the last pre-ESRD serum calcium measurement and the date of dialysis initiation was 19 (interquartile range 3 to 69) days. Compared with excluded patients who did not have available data on albumin-corrected serum calcium (cSCa), included patients were younger; less likely to be female, white, and married; more likely to be black and divorced; and had higher prevalences of diabetes and depression (absolute standardized difference >0.1; Supplemental Table S1).

Among included patients, the mean prelude 6-month averaged cSCa was 9.3 ± 0.7 mg/dL. Patients with higher cSCa were older; more likely to be white and married; had higher Charlson comorbidity index scores; and had higher prevalences of cardiovascular diseases, chronic pulmonary diseases, and cancer (Table 1). They also had higher levels of estimated GFR, hemoglobin, and serum bicarbonate, and had lower prevalences of calcium supplement, nutritional vitamin D, erythropoiesis-stimulating agent, and sodium bicarbonate use in the 6-month prelude period. There was a U-shaped or reversed U-shaped association of cSCa with active vitamin D, renin-angiotensin-aldosterone system inhibitors, and calcium-containing phosphorus binders.

Predictors of low (<8.5) and high (>10.0 mg/dL) corrected serum calcium concentrations

After adjustment for demographics, Charlson comorbidity index, comorbidities, BMI, and estimated GFR, factors associated with low cSCa were younger age; male sex; non-white races; Hispanic ethnicity; lower levels of estimated GFR, hemoglobin, and serum bicarbonate; higher serum albumin; and the baseline use of calcium supplement, active vitamin D, erythropoiesis-stimulating agents, and sodium bicarbonate (Table 2). Married status, history of ischemic heart disease, cancer, and the use of renin-angiotensin-aldosterone system inhibitors were associated with lower likelihood of hypocalcemia. Many of those variables showed an inverse association with high cSCa, but the associations of black race, estimated GFR, and the use of renin-angiotensin-aldosterone system inhibitors were not significant for hypercalcemia. Diabetes, nutritional vitamin D, and diuretics showed lower likelihood of having high cSCa but was not associated with low cSCa, whereas active vitamin D use was associated with both low and high cSCa.

Trajectories of corrected serum calcium before and after dialysis initiation

In the pre-ESRD period, patients who had lower prelude 6-month averaged cSCa showed a steeper decreasing trend in cSCa, whereas those with 6-month pre-ESRD averaged cSCa of ≥10.0 mg/dL had an increasing trend (Fig. 1). There was a rapid correction in cSCa toward the normal range after dialysis initiation, and the differences in cSCa across groups were attenuated but maintained in the post-ESRD period.

Pre-ESRD corrected serum calcium and post-ESRD mortality

A total of 9596 patients died during the follow-up period (mean 1.9 years; total 41,541 patient-years) with an incidence rate of 23.1 per 100 patient-years. There was an incremental mortality risk among patients with higher cSCa, which was slightly attenuated but robust across adjustment models ($p_{trend} < 0.001$ for all adjustments; Fig. 2 and Supplemental Table S2); the adjusted hazard ratios (aHRs [95% CI]) of the lowest (<8.0 mg/dL) and highest (≥10.0 mg/dL) cSCa groups were 0.82 (0.72, 0.94) and 1.28 (1.18, 1.38), respectively, in the primary adjustment model (ie, model 3). The trend in mortality risk across cSCa levels persisted for both cardiovascular and noncardiovascular death ($p_{trend} < 0.01$ in all models), but appeared stronger for noncardiovascular death; the corresponding aHRs (95% CI) for the lowest and highest cSCa groups were 1.03 (0.82, 1.27) and 1.14 (0.99, 1.32) for cardiovascular death, respectively, and 0.72 (0.61, 0.86) and 1.35 (1.23, 1.49) for noncardiovascular death, respectively. Uncorrected calcium showed similar associations after adjustment for serum albumin (ie, models 3

Table 1. Baseline Demographic and Clinical Characteristics of 21,826 US Veterans With ESRD Transitioning to Dialysis Stratified by Prelude 6-Month Averaged Corrected Serum Calcium

Variable	Total	Corrected serum calcium (mg/dL)					
		<8.0	8.0 to <8.5	8.5 to <9.0	9.0 to <9.5	9.5 to <10.0	≥10.0
n (%)	21,826	930 (4)	1279 (6)	3987 (18)	8079 (37)	5467 (25)	2084 (10)
Age (years)	68 ± 11	63 ± 11	66 ± 11	68 ± 11	68 ± 11	68 ± 11	69 ± 11
Female (%)	2	1	1	1	2	3	3
Race (%)							
White	64	46	55	63	66	66	69
Black	31	46	38	31	29	30	28
Other races	5	8	7	6	5	4	3
Hispanic (%)	8	11	11	10	8	6	5
Marital status (%)							
Single	9	14	11	9	9	8	8
Married	53	41	48	52	53	55	58
Divorced	28	36	31	29	28	27	24
Widowed	10	9	10	10	10	9	10
Charlson comorbidity index	4 (2, 5)	3 (1, 4)	3 (2, 5)	4 (2, 5)	4 (2, 5)	4 (2, 6)	4 (2, 6)
Comorbidities (%)							
Diabetes	70	65	70	71	70	71	66
Ischemic heart disease	53	33	44	51	55	56	58
Congestive heart failure	50	34	42	49	52	53	54
Atrial fibrillation	14	6	11	12	15	15	16
Cerebrovascular disease	28	18	24	27	29	29	29
Chronic pulmonary disease	38	25	32	37	39	41	42
Cancer	22	15	18	21	22	23	27
Depression	28	24	26	27	28	29	26
Body mass index (kg/m^2)	30.2 ± 6.8	30.0 ± 6.9	29.9 ± 6.9	29.9 ± 6.7	30.2 ± 6.8	30.5 ± 6.9	30.3 ± 7.1
Estimated GFR (mL/min/1.73m^2)	10 (7, 13)	7 (5, 9)	8 (6, 11)	9 (7, 12)	10 (7, 13)	10 (7, 14)	10 (7, 13)
Laboratory tests							
Hemoglobin (g/dL)	10.5 ± 1.6	9.6 ± 1.5	9.9 ± 1.4	10.2 ± 1.5	10.5 ± 1.6	10.7 ± 1.7	10.8 ± 1.7
Albumin (g/dL)	3.4 ± 0.6	3.4 ± 0.5	3.4 ± 0.6	3.4 ± 0.5	3.4 ± 0.6	3.3 ± 0.7	3.3 ± 0.7
Corrected serum calcium (mg/dL)	9.3 ± 0.7	7.4 ± 0.5	8.3 ± 0.1	8.8 ± 0.1	9.3 ± 0.1	9.7 ± 0.1	10.4 ± 0.5
Bicarbonate (mEq/L)	23 ± 4	20 ± 4	21 ± 4	22 ± 4	23 ± 4	24 ± 4	24 ± 4
Baseline medication use (%)							
Calcium supplement	19	46	32	21	17	15	14
Active vitamin D	32	41	37	33	29	31	37
Nutritional vitamin D	27	27	32	30	28	26	21
Non-calcium-containing phosphate binders	19	21	20	19	18	20	23
Erythropoiesis stimulating agents	30	36	37	34	28	27	26
RAAS inhibitors	45	35	39	43	46	48	44
Sodium bicarbonate	27	38	35	32	26	24	22
Loop diuretics and/or thiazide	75	72	76	74	75	75	72

GFR = glomerular filtration rate; RAAS = renin-angiotensin-aldosterone system.

Values are expressed as mean ± SD, median (IQR), or percentage, as appropriate. SI conversion factors: To convert hemoglobin to g/L, multiply by 10; albumin to g/L, multiply by 10; calcium to mmol/L, multiply by 0.25; bicarbonate to mmol/L, multiply by 1.0.

and 4; Supplemental Fig. S2). Cox models using restricted cubic spline functions showed consistent results between white and black patients for all-cause, cardiovascular, and noncardiovascular death (Supplemental Fig. S3). Similarly, the association of cSCa with all-cause mortality was consistent across subgroup analyses based on age, diabetes, estimated GFR at dialysis initiation, history of ischemic heart disease, history of congestive heart failure, serum albumin, and body mass index (Supplemental Fig. S4).

To evaluate the effect modification by calcium-raising drugs, we included the interaction terms of sSCa with calcium supplement and active vitamin D together in the primary model for all-cause mortality. The interaction term was significant for active vitamin D ($p_{interaction} < 0.001$) but not for calcium supplement ($p_{interaction} = 0.48$). These findings were consistent with stratified analyses based on either calcium supplement or active vitamin D use. Higher cSCa concentrations were associated with higher all-cause mortality irrespective of calcium supplement use ($p_{trend} < 0.001$ for both; Fig. 3*A* and Supplemental Table S3). In contrast, the mortality risk associated with cSCa ranges exceeding 9.0 mg/dL was attenuated with active vitamin D use (Fig. 3*B*). These findings were further supported by the stratified analyses according to (1) calcium supplement but no active vitamin D, (2) active vitamin D but no calcium supplement, (3) both calcium supplement and active vitamin D, and (4) none of them (Supplemental Fig. S5).

Table 2. Adjusted Odds Ratio for Having Low (<8.5 mg/dL) and High (>10.0 mg/dL) Prelude 6-Month Averaged Corrected Serum Calcium (Reference, 8.5 to 10.0 mg/dL) among 21,826 US Veterans With Late-Stage Chronic Kidney Disease Transitioning to Dialysis in Model 3

	Low (<8.5 mg/dL)			High (>10.0 mg/dL)		
Variable	OR	(95% CI)	*p* Value	OR	(95% CI)	*p* Value
Age (per 10 years)	0.87	(0.83–0.91)	<0.001	1.13	(1.07–1.20)	<0.001
Female	0.31	(0.20–0.47)	<0.001	1.75	(1.34–2.29)	<0.001
Race						
White	Reference			Reference		
Black	1.39	(1.25–1.54)	<0.001	0.93	(0.83–1.04)	0.22
Other races	1.40	(1.15–1.69)	<0.001	0.65	(0.49–0.86)	0.002
Hispanic	1.57	(1.34–1.84)	<0.001	0.63	(0.51–0.79)	<0.001
Marital status						
Married	Reference			Reference		
Single	1.25	(1.07–1.46)	0.004	0.91	(0.76–1.09)	0.28
Divorced	1.18	(1.06–1.31)	0.002	0.82	(0.73–0.93)	0.001
Widowed	1.33	(1.13–1.57)	<0.001	0.81	(0.69–0.96)	0.01
Charlson comorbidity index	0.98	(0.95–1.02)	0.36	0.99	(0.96–1.03)	0.74
Comorbidities						
Diabetes	1.12	(0.99–1.26)	0.07	0.79	(0.70–0.89)	<0.001
Ischemic heart disease	0.80	(0.72–0.90)	<0.001	1.13	(1.01–1.26)	0.04
Congestive heart failure	0.93	(0.83–1.05)	0.22	1.02	(0.91–1.15)	0.75
Atrial fibrillation	1.01	(0.86–1.19)	0.88	1.01	(0.88–1.15)	0.92
Cerebrovascular disease	0.93	(0.82–1.05)	0.22	0.96	(0.85–1.08)	0.52
Chronic pulmonary disease	0.99	(0.88–1.11)	0.85	1.01	(0.91–1.13)	0.82
Cancer	0.86	(0.74–1.00)	0.04	1.20	(1.04–1.38)	0.01
Depression	0.91	(0.82–1.02)	0.09	0.94	(0.84–1.05)	0.26
Body mass index (per 5 kg/m^2)	0.97	(0.93–1.00)	0.08	1.04	(1.00–1.08)	0.04
Estimated GFR (per 5 mL/min/1.73m^2)	0.56	(0.52–0.59)	<0.001	1.01	(0.98–1.04)	0.38
Laboratory tests						
Hemoglobin (g/dL)	0.75	(0.72–0.77)	<0.001	1.16	(1.13–1.20)	<0.001
Albumin (g/dL)	1.23	(1.13–1.33)	<0.001	0.69	(0.63–0.74)	<0.001
Bicarbonate (mEq/L)	0.85	(0.84–0.87)	<0.001	1.08	(1.07–1.10)	<0.001
Baseline medication use						
Calcium supplement	2.72	(2.46–3.01)	<0.001	0.75	(0.65–0.86)	<0.001
Active vitamin D	1.24	(1.13–1.36)	<0.001	1.44	(1.31–1.59)	<0.001
Nutritional vitamin D	1.08	(0.97–1.19)	0.15	0.72	(0.64–0.81)	<0.001
Non-calcium-containing phosphate binders	0.93	(0.83–1.04)	0.19	1.42	(1.27–1.59)	<0.001
Erythropoiesis stimulating agents	1.28	(1.17–1.41)	<0.001	0.91	(0.82–1.01)	0.08
RAAS inhibitors	0.73	(0.67–0.81)	<0.001	0.94	(0.85–1.03)	0.17
Sodium bicarbonate	1.34	(1.22–1.48)	<0.001	0.81	(0.72–0.90)	<0.001
Loop diuretics and/or thiazide	1.09	(0.98–1.22)	0.13	0.89	(0.80–1.00)	0.04

OR = odds ratio; CI = confidence interval; GFR = glomerular filtration rate; RAAS = renin-angiotensin-aldosterone system.

SI conversion factors: To convert hemoglobin to g/L, multiply by 10; albumin to g/L, multiply by 10; calcium to mmol/L, multiply by 0.25; bicarbonate to mmol/L, multiply by 1.0.

These associations appeared consistent and even stronger for noncardiovascular death than for cardiovascular death (Fig. 3*D–F* and Supplemental Table S3). For cardiovascular mortality, there was an association with cSCa among patients without the use of either calcium supplement or active vitamin D ($P_{trend} = 0.003$ and 0.002, respectively), and no significant association was observed across cSCa concentrations among their counterparts ($P_{trend} = 0.47$ and 0.39, respectively).

Pre-ESRD change in corrected serum calcium and post-ESRD mortality

A total of 16,349 patients (75%) had available data for calculating slope in cSCa concentrations during the pre-ESRD period. Median rate of decline in cSCa was –0.15 (interquartile range –0.39 to 0.07) mg/dL/year. In the unadjusted model, patients with faster decline in cSCa showed lower mortality overall and irrespective of first available cSCa concentrations during the 1-year prelude period ($p_{interaction} = 0.66$; $p_{trend} < 0.001$ for all; Fig. 4 and Supplemental Table S4). The relationship between faster cSCa decline and lower mortality was robust against adjustment among patients with first available cSCa levels of 9.0 to <9.5 mg/dL and ≥9.5 mg/dL ($p_{trend} < 0.01$ for both), whereas it was gradually attenuated and lost its significance, but not reversed, by the hierarchical adjustments if the first available cSCa was <9.0 mg/dL. Cox models using restricted cubic spline functions confirmed consistent results for noncardiovascular mortality, but there was no significant association between the rate of decline in cSCa and cardiovascular mortality (Supplemental Fig. S6). When stratifying patients by medication use, faster decline in cSCa

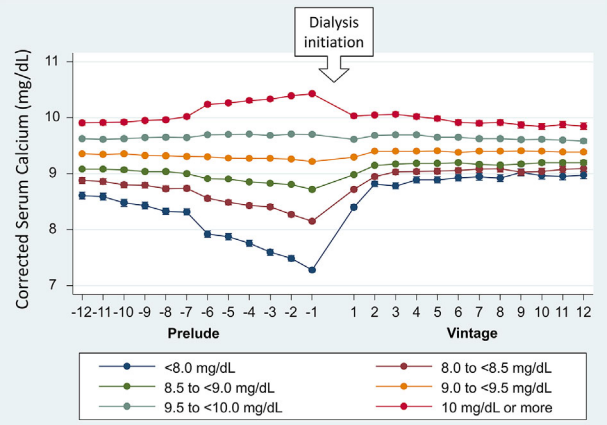

Fig. 1. Trajectories of monthly population mean corrected serum calcium concentrations during the pre- and post-end-stage renal disease 12 months across six groups based on averaged values over the prelude 6 months.

was associated with lower mortality risk among patients without the use of calcium supplement or active vitamin D but not among their counterparts in the primary model (Supplemental Fig. S7; $p_{interaction} = 0.03$ and 0.001, respectively).

Discussion

In this large, contemporary, and national cohort of VA patients with incident ESRD, we found a linear relationship between lower pre-ESRD cSCa and greater post-EDSR survival, even in lower than normal cSCa concentrations. Consistent findings were observed between white versus black races and between patients with versus without calcium supplement use. However, the risk associated with higher cSCa concentrations were attenuated among active vitamin D users. Faster decline in cSCa was also associated with lower mortality among patients with the first available cSCa $\geq$9.0 mg/dL during the 1-year pre-ESRD period. These relationships between decline in cSCa and mortality were not observed among calcium supplement users or active vitamin D users. Both serum levels and decline rates of cSCa consistently showed a stronger association with for noncardiovascular rather than cardiovascular mortality.

Few studies have examined the association between cSCa and mortality in non-dialysis-dependent patients. Findings have been mixed, in part because of varying study populations, adjustment covariates, and statistical modeling approaches; in addition, varying degrees of kidney function across the study cohorts may have contributed to heterogeneous results. For example, one study showed a U-shaped association among patients with estimated GFR >60 mL/min/1.73m^2.[22] Another cohort study, where the median estimated creatinine clearance was 45 mL/min, found no association between cSCa and mortality.[23] In contrast, Kovesdy and colleagues found an increased long-term mortality risk associated with higher cSCa among patients with mean estimated GFR of 33 mL/min/1.73m^2.[15] A similar tendency was noted among patients with stage 4–5 CKD,[24] albeit not significant because of the limited statistical power. We examined a large cohort of patients with incident ESRD and demonstrated the consistent association between higher pre-ESRD cSCa and higher post-ESRD mortality. These observations

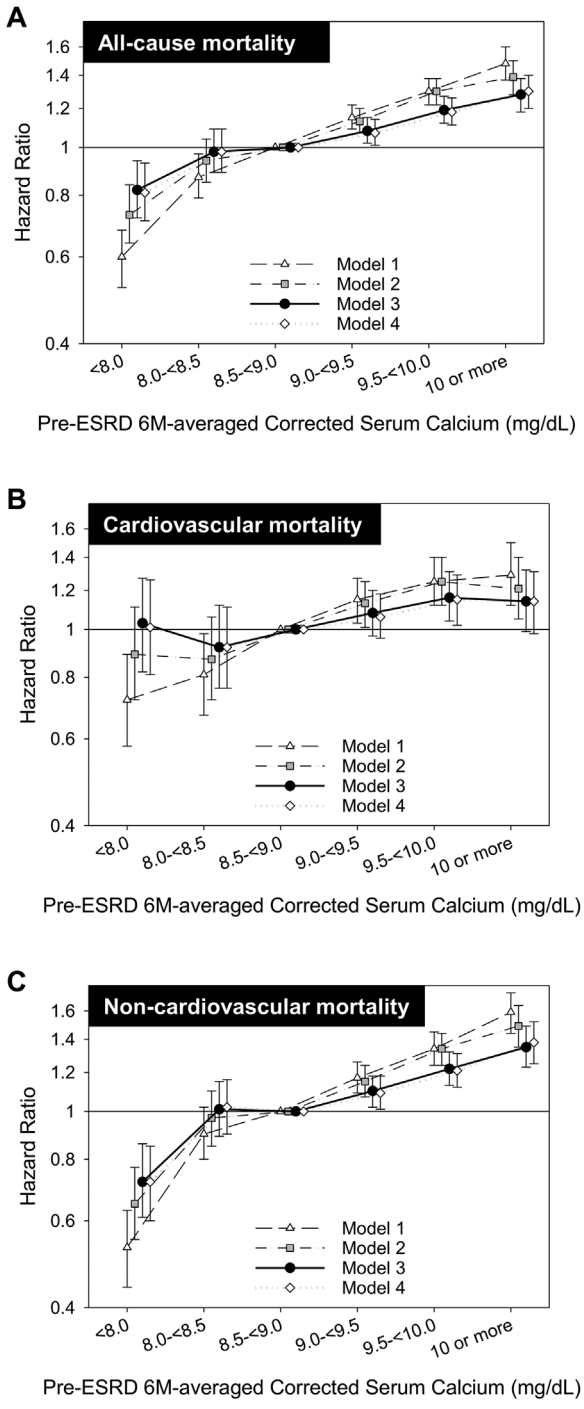

Fig. 2. Association between 6-month averaged corrected serum calcium concentrations before dialysis initiation and (*A*) all-cause, (*B*) cardiovascular, and (*C*) noncardiovascular mortality with hierarchical adjustments for demographics, comorbidities, medications, body mass index, estimated glomerular filtration rate, serum albumin, and medications.

were further supported by the mortality risk associated with increasing cSCa.

Main mechanisms underlying hypercalcemia and mortality in CKD have been suggested, including vascular calcification, which may eventually lead to cardiovascular death.[11–13]

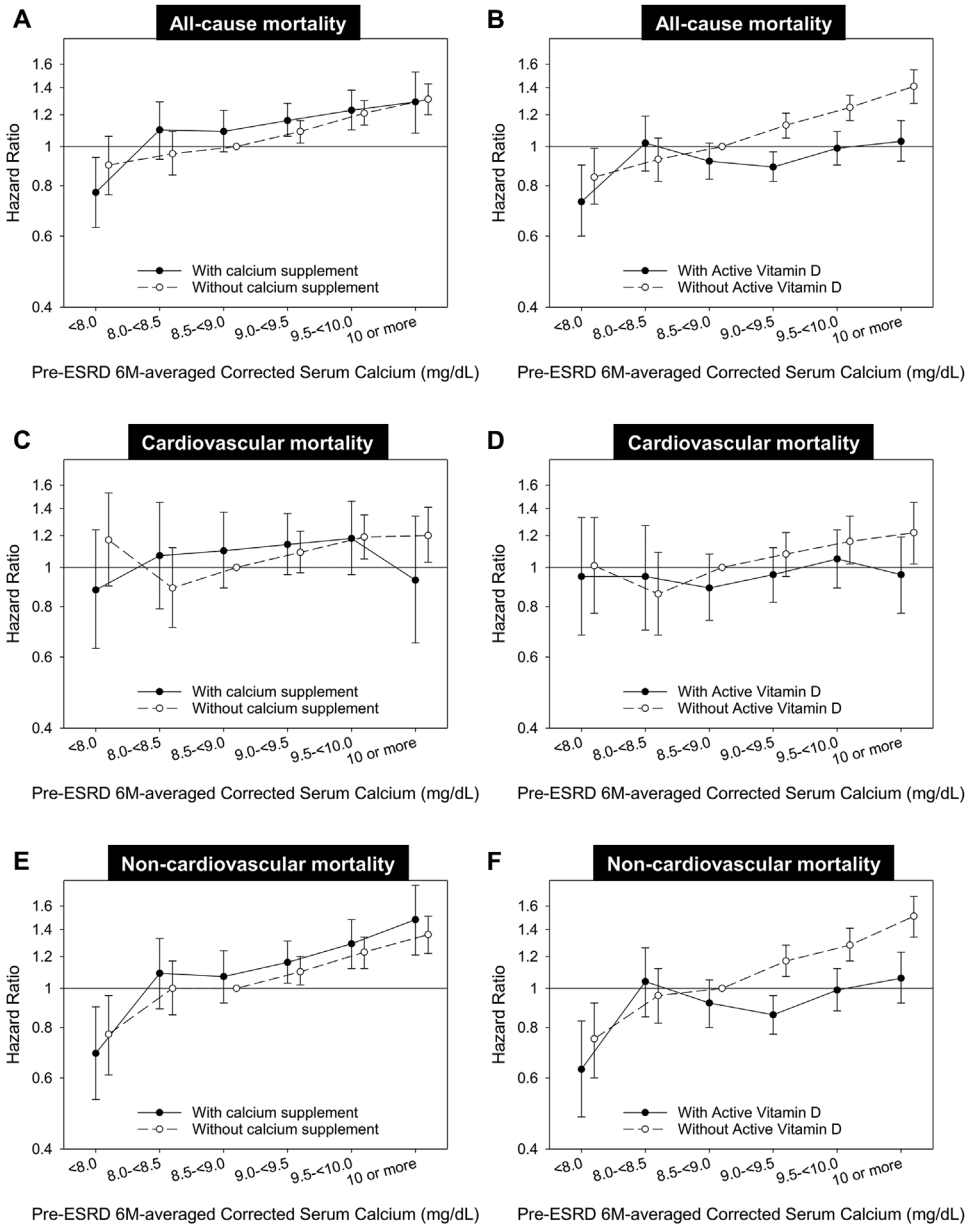

Fig. 3. Adjusted association of 6-month averaged corrected serum calcium before dialysis initiation with all-cause, cardiovascular, and noncardiovascular mortality in model 3, stratifying patients into 12 groups according to six corrected serum calcium levels and the use of either calcium supplement (*A*, *C*, and *E*) or active vitamin D (*B*, *D*, and *F*).

Indeed, non-calcium-containing phosphorous binders, compared with calcium-containing binders, have been shown to lower risk of the development of hypercalcemia,[25] progression of arterial calcification,[26–30] hospitalization,[31] and mortality[25,26] among dialysis patients. A small randomized clinical trial also suggested the survival benefit of non-calcium-containing versus calcium-containing phosphorous binders in non-dialysis-dependent CKD.[32] However, several meta-analyses have pointed out that evidence supporting the cardiovascular benefit of non-calcium-based phosphate binders are lacking in terms of clinical outcomes such as hospitalization and mortality.[25–27] Our results provided further evidence that the association between pre-ESRD cSCa and mortality may be stronger for noncardiovascular versus cardiovascular death after dialysis initiation. This is plausible given that cardiovascular events are among causes of protein-energy wasting in this population, leading to various adverse consequences including cardiorenal syndrome, infection, decreased physical function, and loss of residual kidney function.[33–35] Additionally, macrocalcification (ie, medial artery calcification), which is frequently observed among patients with advanced CKD, can develop without occlusion of vasculature; hence, increased vascular stiffness due to vascular calcification in CKD may not necessarily result in cardiovascular events.

Hypocalcemia adversely affects cardiac function and rhythm, possibly leading to death through heart failure and arrhythmias,[36,37] and previous studies have shown the relationship between low cSCa and high mortality in various populations.[8,16,22] However, clinical symptoms depend on both the

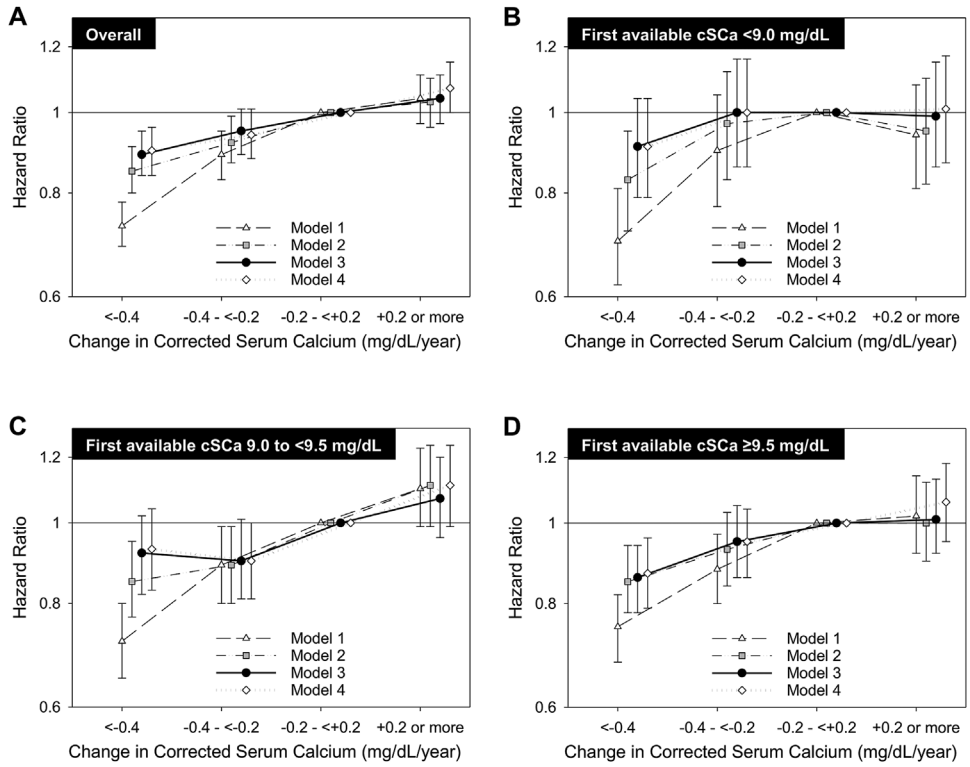

Fig. 4. Distributions and restricted cubic splines comparing all-cause mortality risk associated with 12-month change in corrected serum calcium (cSCa) before dialysis initiation across adjustment models (models 1–4), stratified by the first available cSCa during the 1-year pre-ESRD period (*A*, overall; *B*, <9.0 mg/dL; *C*, 9.0 to <9.5 mg/dL; and *D*, ≥9.5 mg/dL).

severity and chronicity of hypocalcemia. Even very low ionized calcium levels can be asymptomatic in chronic hypocalcemia,[38] and cSCa gradually declines along with kidney function in the later stages of CKD as shown in our study. Also, calcium status may be underestimated in late-stage CKD because the fraction of ionized calcium increases according to metabolic acidosis.[39–41] These factors observed in late-stage CKD may diminish the mortality risk of hypocalcemia, resulting in the incremental association between cSCa and mortality. Additionally, time-dependent Cox models may be preferred to evaluate the short-term association with mortality if repeated cSCa measurements were available during the follow-up period.[15]

The proportion in the final analytical cohort was low ($n = 21,826$; 34%) when compared with the original cohort of 64,930 patients, which may raise a concern about selection bias. However, the number of patients with available data on pre-ESRD estimated GFR was also limited in the administrative VA database ($n = 26,209$; 40%), suggesting that many veterans primarily received pre-ESRD care outside of the VA health care system. A total of 24,227 patients (37%) had available data on pre-ESRD serum calcium (Supplemental Fig. S1), and the difference in the numbers of patients with available pre-ESRD eGFR ($n = 26,209$) versus those included in this study ($n = 21,826$) was primarily attributable to our definition of corrected serum calcium where serum calcium and albumin had to be measured concomitantly. Therefore, our cohort is considered a majority of veterans receiving care within the VA health care system during the pre-ESRD period.

The baseline use of active vitamin D attenuated the mortality risk associated with higher cSCa concentrations in this study, particularly for noncardiovascular death. Vitamin D is suggested to have various pleiotropic effects against various nonskeletal diseases including CKD, diabetes, malignancies, infectious diseases, and cardiovascular diseases,[2,42–44] and several observational studies have shown the association of active vitamin D treatment with favorable clinical outcomes among patients with CKD and ESRD.[45–50] The attenuation in the risk of noncardiovascular mortality by baseline active vitamin D use was observed only among patients with pre-ESRD cSCa levels >9.0 mg/dL but not among those with lower cSCa levels. This observation may be explained by older age and higher Charlson comorbidity index among patients with higher pre-ESRD cSCa levels because these factors are associated with both vitamin D deficiency and adverse clinical events. Although randomized clinical trials failed to demonstrate the cardiovascular benefit from active vitamin D in CKD in terms of left ventricular mass and diastolic function,[51,52] a recent observational study found that the association between active vitamin D treatment and mortality was stronger for noncardiovascular than cardiovascular death,[53] which is consistent with our results. However, there might be survivor bias because we defined the medication use based on the baseline period (ie, prevalent users), not the initial period after dialysis initiation (ie, new users). Baseline serum cSCa levels had also been increased to some extent by active vitamin D among prevalent users, and hence, the relative effects of active vitamin D, compared with other calcium-raising drugs such as calcium supplements, still need to be evaluated in clinical trials among patients with advanced CKD with a focus on noncardiovascular adverse events.

We acknowledge several other limitations in this study. By nature of this being an observational study, we could not make definitive statements about the causal associations of cSCa and medications with mortality. We are also not able to exclude the possibility of residual confounding and the presence of unmeasured confounders. We did not include serum phosphorus because of the inverse or reciprocal correlation between serum calcium and phosphorus and because of the high degree of missing data. This is likely bias toward the null leading to the underestimation of risk-associated higher cSCa given the established relationship between higher serum phosphorus and higher mortality in CKD.[54] Additionally, there are likely to be misclassifications of cause of death in the administrative records, which would have diluted the difference between the associations of serum calcium with cause-specific deaths. Furthermore, recent studies have shown that the correlation between cSCa and ionized calcium is inadequate among both dialysis patients and non-dialysis-dependent patients with CKD.[40,55,56] More accurate assessment of calcium status may alter the strength in the associations for cardiovascular and noncardiovascular mortality.[57] We also cannot exclude the possibility of selection bias resulting from our inclusion criteria of patients who survived the pre-ESRD to post-ESRD transition periods. Lastly, this study cohort mainly consisted of non-Hispanic white males or non-Hispanic black males, and hence, our findings may not be extrapolated to females, Hispanics, or other races.

In conclusion, our study demonstrated an incremental linear association of higher pre-ESRD cSCa with higher post-ESRD mortality among patients with incident ESRD, especially for noncardiovascular death. The mortality risk associated with higher cSCa was attenuated among active vitamin D users. These observations are in contrast to the current clinical practice guidelines suggesting maintaining total serum calcium concentrations within the normal range across stages 3–5D CKD. Our findings are hypothesis generating, and further studies are necessary to explore the optimal management of serum calcium in late-stage CKD.

Disclosures

KK-Z has received honoraria and/or support from Abbott, Abbvie, Alexion, Amgen, American Society of Nephrology, AstraZeneca, Aveo, Chugai, DaVita, Fresenius, Genetech, Haymarket Media, Hospira, Kabi, Keryx, National Institutes of Health, National Kidney Foundation, Relypsa, Resverlogix, Sanofi, Shire, Vifor, and ZS-Pharma. Obi has received honoraria from Ono and Chugai. All other authors state that they have no conflicts of interest.

Acknowledgments

CPK, KK-Z, and ES are employees of the VA. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as official policy or interpretation of the VA or the US government.

The work in this article has been performed with the support of the National Institute of Diabetes, Digestive and Kidney Disease (NIDDK) of the National Institute of Health research grants U01-DK102163. YO is supported by the Uehara Memorial Foundation Research Fellowship. KK-Z is supported by K24-DK091419, as well as philanthropic grants from Mr Harold Simmons, Mr Louis Chang, Dr Joseph Lee, and AVEO. CMR is supported by the NIDDK grant K23-DK102903.

Authors' roles: Study design: YO and KK-Z. Study conduct: YO, CPK, and KK-Z. Data collection: KK-Z and CPK. Data analysis: YO, CP, MS, and ES. Data interpretation: YO, KS, TH, CMR, CPK, and KK-Z. Drafting manuscript: CP and YO. Revising manuscript content: MS, ES, KS, TH, CMR, CPK, and KK-Z. Approving final version of manuscript: YO, CP, MS, ES, KS, TH, CMR, CPK, and KK-Z. YO and ES take responsibility for the integrity of the data analysis.

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